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(54) Title: SLOW RELEASE VITREOUS SYSTEMS

(57) Abstract

The invention provides a slow release vitreous system comprising a water soluble glass having a softening point of less than 320°C and preferably less than 200°C wherein said water soluble glass has dissolved or admixed therein an active agent such as a pharmaceutical which is stable at the melting point of the glass and which releases to an aqueous environment of use over a predetermined time period.

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SLOW RELEASE VITREOUS SYSTEMS

5 The present invention relates to slow-release vitreous systems particularly for the release of biologically active materials to an aqueous environment of use over a predetermined time period.

10 Slow-release systems are well known in the art but tend to be specialised because of their inherent expense. Slow-release systems are for example used in the pharmaceutical industry for the administration of biologically active agents to a patient over a predetermined time span at a constant or varying rate depending upon the circumstances. Other slow-release
15 systems are known for other purposes, but all suffer from the inherent expense or lack of flexibility of the slow-release vehicle.

20 Glass is a relatively cheap material, and the glasses which are water soluble are known. Indeed phosphate glasses have been used to release inorganic substances which are thermostable since the softening point of phosphate glasses is for example 400 - 500°C. These

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phosphate glasses have a widely varying dissolution rate depending upon the precise constitution of the watersoluble glass chosen and are hence able to transmit inorganic salts to an environment of use over
5 a predetermined time period.

Low melting point water soluble glasses for example the acetate glasses have been described in The Journal of the American Ceramic Society Vol 52, No. 4 April
10 1969 Pages 224-225. Further nitrate glasses have been described, as such, in the Journal of The Chemical Society 1969 pages 2398 et seq. It has not however been appreciated that the combination of the low softening point of the acetate and other
15 carboxylates and nitrate type glasses combined with their variable water solubility provides an excellent slow release vehicle for heat-sensitive substances, such as biologically active substances, to an aqueous environment of use.

20

GB-A-2,182,034 discloses a vitreous system in which organic materials are incorporated in a water soluble glass by forming a sintered porous body and filling the same with an organic material in liquid form.

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This disclosure teaches against incorporating organic materials directly into the glass.

5 According therefore to the present invention there is provided a slow release vitreous system comprising a water soluble glass having a softening point of less than 320°C characterised in that said water soluble glass has dissolved, or admixed therein, an active agent which releases to an aqueous environment of use
10 over a predetermined time period.

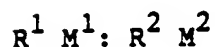
Where "glass" describes amorphous material derived for example from carboxylates and nitrates. The active agents, which can be biologically active or
15 nonbiologically active, need be stable only to the temperature of the softening point of the glass (see Table 1). This illustrates the advantages of these glasses: compounds with low decomposition temperatures can be safely entrapped or dissolved with little
20 decomposition.

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In a preferred form of the invention the water soluble glass is a carboxylate, nitrate, sulphate or bisulphate glass having a low softening point, e.g. below 200°C.

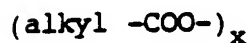
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The glass may be selected from a compound of the formula



10

wherein R^1 and R^2 are the same or different and are selected from



15

wherein x has a value of 1 - 3;

and wherein M^1 and M^2 are the same or different and are selected from H, an alkali metal or an alkaline earth metals or a chemically appropriate metal such as lead or zinc.

20

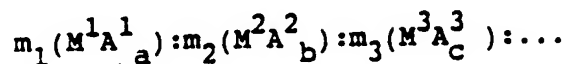
- 5 -

In a preferred embodiment of the foregoing formula; R^1 and R^2 may be $CH_3 COO^-$; the preferred substituent for M^1 and M^2 are lithium, sodium, potassium, calcium, lead or zinc.

5

In a further aspect of the invention the glass selected is made from either a single salt or a mixture of salts or a mixture of salts and acids having general formula

10



15

wherein M^1 , M^2 , $M^3...$ are the same or different and are selected from H, alkali metals or alkaline earth metals or a chemically appropriate metal such as zinc or lead wherein A^1 , A^2 , $A^3...$ are the same or different and are selected from carboxylates preferably chiral carboxylates, such as tartrates nitrate, sulphate or bisulphate; wherein a, b, c ...

20

depend on the valencies of M^1 , M^2 , $M^3...$ and A^1 , A^2 , $A^3...$; wherein m_1 , m_2 , $m_3...$ are the same or

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different.

The invention is further characterised by a method for the production of a slow-release system which method
5 comprises;

selecting a water soluble glass having an appropriate softening point below 320°C and preferably below 200°C; carefully heating said selected glass to its softening
10 temperature,

causing said softened glass to come into intimate contact with an active agent thereby to cause the active agent to be dissolved by, or be admixed
15 therein,

subsequently cooling said system; whereby on exposure of the cooled system to an aqueous environment of use, the glass dissolves to release the active agent over a
20 predetermined time period.

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The glasses as just described may be coated with a coating material to further modify the slow-release rate of the active agent to the environment of use. The shape and geometry of the water soluble glass may also be adjusted to alter the release rates.

The coating material as just described may be a phosphate glass or any selected polymeric material so chosen as to give a desired rate of agent release (see Table 2 below).

The geometry of the system in accordance with the present invention is important. It will be appreciated that the larger the system particle, the smaller the total surface area and hence the slower the release rate in aqueous environment of use. Thus physically relatively large slow-release systems in accordance with the present invention will release the active agent to the environment of use slower than small particles. Thus the constant release rate to an environment of use can be achieved over a long time period by not only selecting the materials from which the release systems are made, but also by altering the

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relative particle sizes in a mixture applied to an environment of use.

5 Further the geometry of the slow-release system in accordance with the present invention may be configured to adjust the output rate of the active agent to an environment of use by altering the rate at which readily soluble glass is exposed for dissolution. Thus for example it is possible to form
10 a multi-layer system wherein layers of the water soluble glass in accordance with the present invention are overlaid by a phosphate glass or other polymeric material. It will be appreciated that the relative thicknesses of the layers can be adjusted to achieve a
15 desired dissolution rate.

Alternatively a multi-layer system may be achieved by providing a central core of the water soluble glass in accordance with the present invention, overlaid by,
20 for example, a coating of a phosphate glass. The relative diameter of the central core which need not be uniform throughout its length, can be adjusted to provide a desired predetermined dissolution rate.

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The active agents in accordance with the present invention may for example be pharmaceutically active agents such as hormones and amino-acids, for administration to agriculturally significant animals for example to ruminants. Alternatively the active agents may be any suitable pharmaceutical agent such as an antibiotic which can be administered to a patient for slow-release.

Alternatively slow-release systems of the present invention can be provided with pheromones which can be utilized to attract specific insects to a specific site. By way of example the pheromones can be specific to an insect which is a pest on a particular crop. Tomatoes for example can be cleared of insect pests in a closed tomato growing area without application of toxic materials to the plants themselves. Since pheromones are specific to insects of a particular sex as well as a particular type, it is also possible to separate males and females of a particular species by this method.

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In a further aspect of the invention for which a nitrate glass may be used, fertilizers are formed with nitrogen, phosphorus, and potassium for administration to a crop in a seed bed preferably in a single pass operation. Further the slow-release systems in accordance with the present invention of this type may also include insecticides, fungicides, or other pesticides in general which act to protect the crop during its growing season, (about three or four months), without the necessity for regular spraying.

It is envisaged that slow-release systems in accordance of this type will be incorporated into the seed bed at the same time as the seed are sown thereby providing long term protection from pest attack as well as fertilization throughout its growing period.

The invention is also suitable for the slow-release of descaling agents for pipes and boilers and for the slow-release of bactericidal agents to water storage systems for the prevention, for example, of Legionella. The systems in accordance with the

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present invention may also be utilized as wood preservatives for in situ applications.

5 The invention will now be described, by way of illustration only in the following examples of the invention.

Example 1

10 Carboxylate glasses were formed by standard methods to have the following constitution as shown in Table 1.

Table 1

Carboxylate Glasses

5	Glass	Mole Ratio	Softening Temperature °C
	$\text{CH}_3\text{CO}_2\text{Li}:\text{CH}_3\text{CO}_2\text{Na}$	1.33:1	160
	$\text{CH}_3\text{CO}_2\text{K}:(\text{CH}_3\text{CO}_2)_2\text{Ca}$	1:1	270
	$\text{CH}_3\text{CO}_2\text{Na}:(\text{CH}_3\text{CO}_2)_2\text{Ca}$	1:1	310
10	" "	2:1	-
	$\text{CH}_3\text{CO}_2\text{K}:(\text{CH}_3\text{CO}_2)_2\text{Ca}$	2:1	-
	$\text{CH}_3\text{CO}_2\text{Li}:(\text{CH}_3\text{CO}_2)_2\text{Pb}$	1:1	-
	$(\text{CH}_3\text{CO}_2)_2\text{Pb}:\text{CH}_3\text{CO}_2\text{K}$	3:1	-
15	$\text{CH}_3\text{CO}_2\text{Na}:(\text{CH}_3\text{CO}_2)_2\text{Zn}$	1:1	180
	$\text{CH}_3\text{CO}_2\text{K}:(\text{C}_2\text{H}_5\text{CO}_2)_2\text{Ca}:\text{C}_4\text{H}_9\text{CO}_2\text{Na}$	1:1:1	150
	$\text{CH}_3\text{CO}_2\text{K}:(\text{CH}_3\text{CO}_2)_2\text{Ca}:\text{C}_7\text{H}_{15}\text{CO}_2\text{Na}$	2:2:1	150
	$(\text{CH}_3\text{CO}_2)_2\text{Ca}:\text{C}_{15}\text{H}_{31}\text{CO}_2\text{Na}$	3:4	150

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Glasses of this type were softened to their softening temperatures and active lactones and esters were incorporated thereinto. These were subsequently recovered from the carboxylate glasses so formed by
5 dissolving the same in an aqueous solution and extracting the target substance from the solution so formed. It was found that the lactones and esters were substantially recoverable.

10 Selected carboxylate glasses of Table 1 in the form of a rod were then coated with a phosphate glass in accordance with Table 2.

Table 2Examples of
Phosphate coatings

Glass Composition	Ratio	Softening Temperature °C	Dis- solution Rate*
$\text{Na}_2\text{O}:\text{P}_2\text{O}_5$	1:1	440	24 mins
$\text{Na}_2\text{O}:\text{CaO}:\text{P}_2\text{O}_5$	2:2:3	-	8 hrs 20 mins
$\text{K}_2\text{O}:\text{CaO}:\text{P}_2\text{O}_5$	2:2:3	560	5 days
$\text{K}_2\text{O}:\text{CaO}:\text{P}_2\text{O}_5$	4:2:5	480	1 hr 10 mins
$\text{K}_2\text{O}:\text{Na}_2\text{O}:\text{P}_2\text{O}_5$	1:2:2	-	14 mins
$\text{Li}_2\text{O}:\text{ZnO}:\text{P}_2\text{O}_5$	1:3:6	<400	31 days
$\text{Li}_2\text{O}:\text{ZnO}:\text{P}_2\text{O}_5$	2:1:7		4.9 days
$\text{Li}_2\text{O}:\text{ZnO}:\text{MgO}:\text{P}_2\text{O}_5$	2:1:0.2:6.8	<400	25 hrs
$\text{Li}_2\text{O}:\text{ZnO}:\text{BaO}:\text{NaF}:\text{P}_2\text{O}_5$	1.95:0.65:0.65: 0.25:6.5	370	
$\text{Na}_2\text{O}:\text{CaO}:\text{MgO}:\text{P}_2\text{O}_5$	4.4:0.6:0.5:4.5	320	No significant loss in weight after 20 hours
$\text{Na}_2\text{O}:\text{ZnO}:\text{P}_2\text{O}_5$	2:1.5:6.5	370	69 days
$\text{Li}_2\text{O}:\text{ZnO}:\text{Na}_2\text{O}:\text{P}_2\text{O}_5$	1:1.5:1.5:6	380	No significant loss in weight after 20 hrs
$\text{MgO}:\text{ZnO}:\text{P}_2\text{O}_5$	0.5:0.5:9	-	-
$\text{K}_2\text{O}:\text{MgO}:\text{ZnO}:\text{P}_2\text{O}_5$	-	-	-

* Rate at which a tablet of glass (1 g, 450-550 mm²) dissolves to 50% of its original mass in 200 mls of water.

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The rod was exposed to the atmosphere at each end of the structure so formed. By selection of the phosphate glasses as shown, a dissolution rate could be adjusted to be between 24 minutes and 70 days.

5 Since the dissolution rate of the acetate glasses is faster than that of the phosphate glasses in general it will be noted that the slow-release system can be adjusted to release its bolus within any desired time frame. Further by altering the relative geometry of
10 the coating and the core it is possible to release more or less active agent to the environment of use over a predetermined portion of the time frame.

The invention therefore comprehends not only a
15 slow-release system and a method for the production thereof, but a method of administering an active agent to an environment of use, said environment of use being agricultural, veterinary, human or industrial.

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CLAIMS

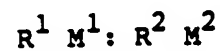
1. A slow release vitreous system comprising a water
soluble glass having a softening point of less than
5 320°C;

characterised in that said water soluble glass has
dissolved or admixed therein an active agent which is
stable at the melting point of the glass and which
releases to an aqueous environment of use over a
10 predetermined time period.

2. A system according to claim 1 characterised in that
the glass is a carboxylate, nitrate, sulphate or
bisulphate glass having a softening point below
15 200°C.

3. A system according to either of claims 1 or 2
characterised in that the glass is selected from a
compound of the formula

20



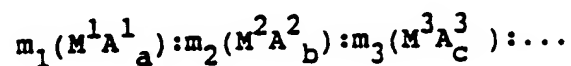
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wherein R^1 and R^2 are the same or different and are selected from (alkyl -COO-)_x wherein x has a value of 1 - 3,

5 and wherein M^1 and M^2 are the same or different and are selected from H, an alkali metal or an alkaline earth metal or a chemically appropriate metal.

10 4. A system according to claim 3 characterised in that the chemically appropriate metal is lead or zinc.

15 5. A system according to either of claims 1 or 2 characterised in that the glass is selected from a single salt or mixture of salts with or without acids of the general formula:



20 wherein M^1 , M^2 , M^3 ... are the same or different and are selected from H, alkali metals or alkaline earth metals or a chemically appropriate metal

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wherein A^1 , A^2 , A^3 ... are the same or different and are selected from carboxylates nitrates, sulphates or bisulphates and

5 wherein a, b, c ... depend upon the valencies of M and A and wherein m_1 , m_2 , m_3 ... are the same or different.

6. A system according to any preceding claim
10 characterised in the vitreous glass as defined is coated with a phosphate glass having a predetermined solution rate.

7. A system according to any preceding claim
15 characterised in that the geometry of the vitreous system is configured to adjust the output rate of the active agent to the aqueous environment of use by adjusting the rate at which readily soluble glass is exposed for dissolution.

20

8. A system according to claim 7 characterised in that the system is a multilayer system comprising layers of water soluble glass according to any of

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claims 1 to 5 overlaid by a phosphate glass of claim 6 or other polymeric material; thereby to adjust rates of dissolution to a desired pattern.

5 9. A system according to claim 7 characterised in that the system is formed of a central core coated with a phosphate glass of claim 6.

10 10. A system according to any preceding claim characterised in that the active agent is selected from a hormone, an amino acid, an antibiotic, a bacteriocide or an agricultural chemical.

15 11. A method for the controlled release of an agricultural, horticultural, or pharmaceutical active agent to an environment of use which comprises delivering such an agent to said environment when dissolved or intimately admixed in a vitreous system according to any of claims 1 to 10.

20 12. A method for the production of a slow-release vitreous system which method comprises:-

selecting a water soluble glass having an appropriate softening point below 320°C, carefully heating said selected glass to its softening temperature,

5 causing said softened glass to come into intimate contact with an active agent thereby to cause the active agent to be dissolved by, or be admixed therein,

10 subsequently cooling said system; whereby on exposure of the cooled system to an aqueous environment of use, the glass dissolves to release the active agent over a predetermined time period.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/GB 90/00497**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : A 61 K 9/20, C 03 C 4/00, C 03 C 3/12																	
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border-bottom: 1px solid black; font-size: small;">Classification System</td> <td style="border-bottom: 1px solid black; font-size: small;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC⁵</td> <td style="border: 1px solid black; padding: 5px;">A 61 K, C 03 C</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched ⁸</div>			Classification System	Classification Symbols	IPC ⁵	A 61 K, C 03 C											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table style="width: 100%; border: none;"> <tr> <th style="width: 10%; font-size: x-small;">Category ¹⁰</th> <th style="width: 70%; font-size: x-small;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; font-size: x-small;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">EP, A, 0009338 (INTERNATIONAL STANDARD ELECTRIC CORPORATION) 2 April 1980 see claims 1,2,3; page 4, lines 10-14; example 1 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-5</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">FR, A, 2521835 (UNIVERSITY OF LEEDS INDUSTRIAL SERVICES) 26 August 1983 see claim 1 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">Chemical Abstracts, vol. 108, 1988 (Columbus, Ohio, US) see page 322, abstract no. 61225x, & SU, A, 1351978 (URAL POLYTECHNIC INSTITUTE) 15 November 1987 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">5</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 3649551 (R.F. BARTHOLOMEW) 14 March 1972 see claims 1-7; column 4, lines 5,6. --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">3,4 ./.</td> </tr> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	EP, A, 0009338 (INTERNATIONAL STANDARD ELECTRIC CORPORATION) 2 April 1980 see claims 1,2,3; page 4, lines 10-14; example 1 --	1-5	X	FR, A, 2521835 (UNIVERSITY OF LEEDS INDUSTRIAL SERVICES) 26 August 1983 see claim 1 --	1	A	Chemical Abstracts, vol. 108, 1988 (Columbus, Ohio, US) see page 322, abstract no. 61225x, & SU, A, 1351978 (URAL POLYTECHNIC INSTITUTE) 15 November 1987 --	5	A	US, A, 3649551 (R.F. BARTHOLOMEW) 14 March 1972 see claims 1-7; column 4, lines 5,6. --	3,4 ./.
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁴ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; font-size: small;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black; font-size: small;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="text-align: center; padding: 5px;">31st July 1990</td> <td style="text-align: center; padding: 5px;">06 SEP 1990</td> </tr> <tr> <td style="border-bottom: 1px solid black; font-size: small;">International Searching Authority</td> <td style="border-bottom: 1px solid black; font-size: small;">Signature of Authorized Officer</td> </tr> <tr> <td style="text-align: center; padding: 5px;">EUROPEAN PATENT OFFICE</td> <td style="text-align: center; padding: 5px;">Mme N. KUIPER </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	31st July 1990	06 SEP 1990	International Searching Authority	Signature of Authorized Officer	EUROPEAN PATENT OFFICE	Mme N. KUIPER							
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/08/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82